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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
OH, TAYLOR V	

ART UNIT	PAPER NUMBER
1625	

DATE MAILED: 03/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

HC

Office Action Summary	Application No.	Applicant(s)	
	10/788,728	ZHU ET AL.	
	Examiner	Art Unit	
	Taylor Victor Oh	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 2/26/04.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-19 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-19 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

The Status of Claims:

Claims 1-19 are pending.

Claims 1-19 have been rejected.

DETAILED ACTION

1. Claims 1-19 are under consideration in this Office Action.

Priority

2. It is noted that this application is a continuation of 10/224,890 filed on 08/19/2002 (US 6,730,809), which claims benefit of 60/315,832 (08/29/2001).

Drawings

3. None.

Specification

The disclosure is objected to because of the following informalities:

In the line 12 of the specification on page 14 , the title of the example " Example 2" is recited. "Example 2 " has already been described in the line 13 of the specification on page 12. Therefore, the examiner recommends to change it to Example 3.

Claim Objections

Claims 4 and 10 and 14 are objected to because of the following informalities:

In claim 4, the phrase " selectively reducing said nitrile moiety to form an amine moiety produces a compound comprising an ester or amide moiety" is recited. This expression is unclear. The examiner recommends to change from that expression to " selectively reducing said nitrile moiety produces an ester or amide moiety". Therefore, appropriate correction is required.

In claim 10, the phrase " the group consisting of :" is recited. The colon " :" is unnecessary. Therefore, appropriate correction is required.

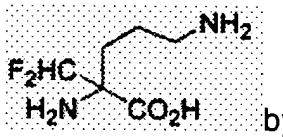
In claim 14, the term" an alkyl4-cyanobutanoate" is recited. There is no space between term "an alkyl" and " 4". Therefore, appropriate correction is required.

Claim Rejections - 35 USC § 112

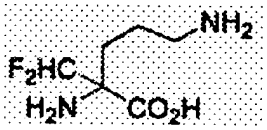
The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8, 10-12, and 16-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

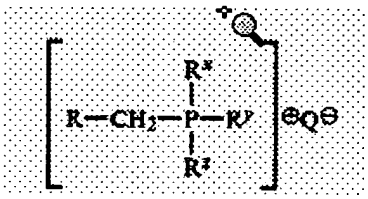
Claims 1-8 and 10-11 have described the process of the preparation of a compound of the formula :  by providing an intermediate compound comprising fluorine and a nitrile moiety and selectively reducing said nitrile moiety to form an amine moiety. In the claim, providing the intermediate compound comprising fluorine and a nitrile moiety is recited. However, there is no general structural chemical formula for the intermediate compound which describes distinguishing identifying characteristics sufficient show that the applicant was in possession of the claimed invention, and the claim ,as a whole, may not be adequately described where the invention is described solely in terms of a process of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. For example, according to the Beatty prior art (US 5,741,955), it discloses a reductive hydrolysis of oligomeric polyfluoroalkane nitrile compound where the formula of the compound is $F(CF_2CF_2)_zCH_2CH_2CN$, wherein z=2 to 6; as a result of the process, a mixture of the corresponding amines and alcohols [$F(CF_2CF_2)_zCH_2CH_2$ CH_2NH_2 and $F(CF_2CF_2)_zCH_2CH_2$

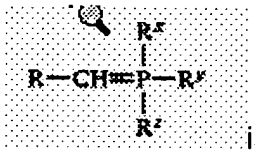
CH_2OH] is formed (see col. 11 , ex. 8, lines 15-32). From this example , it makes clear that the generic description of the intermediate compound comprising fluorine and a nitrile moiety in the claim would not always guarantee to form the applicant's intended final product of

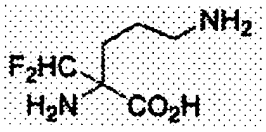


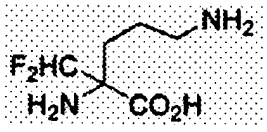
. Therefore, the specification has failed to describe the subject matter in the claims as to the relationship between the intermediate structure of the invention containing fluorine and the nitrile moiety and its function and its role with respect to fluorine and the nitrile moiety in the part of the process of making the desired product.

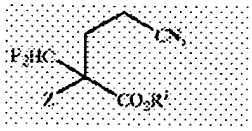
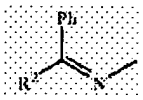
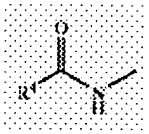
Claims 12 and 16-17 have described the process of the preparation of alpha-difluoromethylornithine by treating a compound with a strong base at a temperature of -35^0 to 25^0 C. In the claim, " treating a compound with a strong base at a temperature of -35^0 to 25^0 C" is recited. However, there is no general structural chemical formula for the compound which describes distinguishing identifying characteristics sufficient show that the applicant was in possession of the claimed invention, and the claim ,as a whole, may not be adequately described where the invention is described solely in terms of a process of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. For example, according to the Jewell et al prior art (US 4,677,211), it discloses the preparation of the Wittig reagents by treating a compound of formula X:

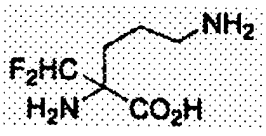


with a strong base at a reduced temperatures from -15^0 to 0^0 C (see col. 5, lines 53-67); as a result,  is formed (col. 5 ,lines 40-45). The reagents and reaction conditions in the prior art are identical with those in the claims; however, as the premises in the claims, treating a compound with a strong base at a temperature of –35^0 to 25^0 C would not always guarantee to form the applicant's intended final product of

 . Therefore, the specification has failed to describe the subject matter in the claims as to the relationship between the reactant compound without its corresponding chemical structure and its function with respect to the reaction conditions during the process of making the desired product.

Claims 1-8 and 10-11 are rejected under 35 U.S.C. 112, first paragraph, because ,while being enabling for a compound of formula  by

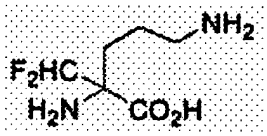
using  as an intermediate, wherein R^1 is linear or branched C^1 to C^4 alkyl and Z is (i) –NH2 or (ii)  wherein R^2 is hydrogen, linear or branched C^1 to C^4 alkyl or aryl , and  , wherein R^4 is linear or branched C^1 to C^4 alkyl, alkoxy or aryl: for examples, ethyl 2-(diphenylmethylene)amino-2-difluoromethyl-4-cyanobutanoate, ethyl 2-benzylideneamino-2-difluoromethyl-4-cyanobutanoate, ethyl 2-amino-2-difluoromethyl-4-cyanobutanoate , or ethyl 2-acetylamino-2-difluoromethyl-4-cyanobutanoate, this description does not reasonably provide enablement for any or all the compounds containing fluorine and a nitrile moiety known in the art. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to include all the compounds unrelated to the currently claimed invention commensurate in scope with these claims.

The specification falls short because data essential for how any intermediate compound containing fluorine and a nitrile moiety would lead to the desired final product  by selectively reducing said nitrile moiety to form an amine moiety.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

The Nature of the Invention

The nature of the invention in claims 1-8 and 10-11 is the process for preparing 

by providing an intermediate compound comprising fluorine and a nitrile moiety and selectively reducing said nitrile moiety to form an amine moiety.

The State of the Prior Art

The state of the prior art is that according to US Patent No. 4,309,442, alpha-DFMO (difluoromethylornithine) has been obtained from the reaction between dibenzaldimine ornithine methyl ester and chlorodifluoromethane at a temperature of 40 to 50^0 C; another prior art (Seki et al, Biosci., Biotech. Biochem., 57(6), 1024-1025, 1993) discloses a preparation of alpha-DFMOL- from OrnOME-2HCl by using an diisocyanato intermediate prepared via the formyl derivative and alkylated with $ClCHF_2$, followed by acid hydrolysis.

According to the third prior art (US 5,741,955), although it does not produce the desired alpha-DFMO by the process, it expressly discloses the same reductive hydrolysis as shown in the claimed process ; for example, oligomeric polyfluoroalkane nitrile compound where the formula of the compound is $F(CF_2CF_2)_zCH_2CH_2CN$, wherein z=2 to 6; as a result of the process, a mixture of the corresponding amines and alcohols [$F(CF_2CF_2)_zCH_2CH_2\ CH_2NH_2$ and $F(CF_2CF_2)_zCH_2CH_2\ CH_2OH$] is formed. As the prior art have been discussed in the above, there is no conclusive data that the generic claimed intermediate compound would be sufficient enough to lead the desired final product..

The predictability or lack thereof in the art

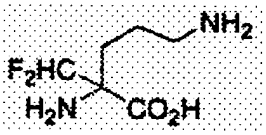
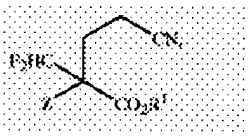
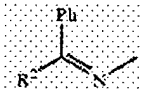
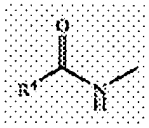
In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art would recognize that any intermediate compound having fluorine and a nitrile moiety without a general structural chemical formula would result in only the uncertainty of the outcome of the process as shown in Beatty (US 5,741,955), which discloses a reductive hydrolysis of oligomeric polyfluoroalkane nitrile compound, where the formula of the compound is $F(CF_2CF_2)_zCH_2CH_2CN$, wherein z=2 to 6; as a result of the process, a mixture of the corresponding amines and alcohols [$F(CF_2CF_2)_zCH_2CH_2\ CH_2NH_2$ and $F(CF_2CF_2)_zCH_2CH_2\ CH_2OH$] is formed, which is not the intended final product of the claimed process. Therefore, the use of a generic phrase "intermediate

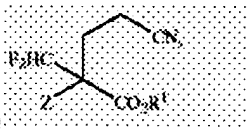
compound having fluorine and a nitrile moiety" can not be translated to the production of the claimed product.

The amount of direction or guidance present

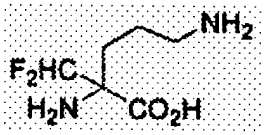
The direction present in the instant specification is that any intermediate compound having fluorine and a nitrile moiety without a general structural chemical formula can be lead to the formation of the desired product. However, the specification is silent and fails to provide guidance as to whether any intermediate compound having fluorine and a nitrile moiety is sufficient enough to allow to form the desired product ; the specification fails to provide a correlation between the structure of the invention and its function. Also, there is no direction and guidance for any intermediate compound having fluorine and a nitrile moiety to be used for the production of the desired final product.

The presence or absence of working examples

There are only six working examples for producing the claimed product formula 1  by using  as the intermediate, wherein R^1 is linear or branched C^1 to C^4 alkyl and Z is (i) –NH2 or (ii)  wherein R^2 is hydrogen, linear or branched C^1 to C^4 alkyl or aryl , and  , wherein R^4 is linear or branched C^1 to C^4 alkyl, alkoxy or aryl.

Furthermore, there are not other working examples for any other intermediates containing fluorine and the nitrile moiety different from  in the specification. Also, the specification fails to provide working examples as to how the other types of intermediates containing fluorine and the nitrile moiety can be resulted in the claimed product, i.e. again, there is no correlation between the intermediate and the desired final product.

The breadth of the claims

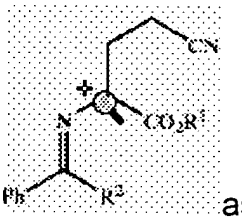
The breadth of the claims is that an intermediate compound comprising fluorine and a nitrile moiety can produce the desired product (formula 1)  by selectively reducing said nitrile moiety to form an amine moiety.

without regarding the affect of the different substituents on the intermediate compound on the desired final product.

The quantity of experimentation needed

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine which one of the intermediates having fluorine and the nitrile moiety would be resulted in the claimed desired compound and would furthermore then have to determine which one of the intermediates having fluorine and the nitrile moiety would not be resulted in the claimed desired compound.

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which intermediates can be employed to produce the desired claimed compound encompassed in the instant claims, with no assurance of success.

Claims 12, and 16-17 are rejected under 35 U.S.C. 112, first paragraph, because ,while , in the process of preparing α-diflurомethylornithine , being enabling for  as a compound to be reacted with a strong base at a temperature of -35^0 to 25^0 C, wherein $R^1 = CH_3CH_2$, $R^2 = H$ in the specification, this description does not reasonably provide enablement for any or all the compounds known in the art. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to include all the compounds unrelated to the currently claimed invention commensurate in scope with these claims.

The specification falls short because data essential for how any compound would lead to the desired final α-diflurомethylornithine product by treating any compound with a strong base at a temperature of -35^0 to 25^0 C.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

The Nature of the Invention

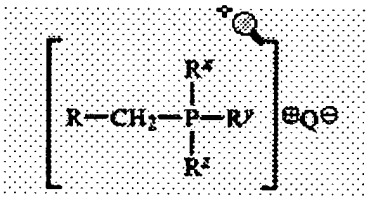
The nature of the invention in claims 12 and 16-17 is the process for preparing α-difluromethylornithine by treating a compound with a strong base at a temperature of -35^0 to 25^0 C.

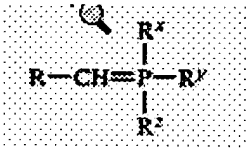
The State of the Prior Art

The state of the prior art is that according to US Patent No. 4,309,442, alpha-DFMO (difluoromethylornithine) has been obtained from the reaction between dibenzaldimine ornithine methyl ester and chlorodifluoromethane at a temperature of 40 to 50^0 C; another prior art (Seki et al, Biosci., Biotech. Biochem., 57(6), 1024-1025, 1993) discloses a preparation of alpha-DFMO from OrnOME-2HCl by using an diisocyanato intermediate prepared via the formyl derivative and alkylated with $ClCHF_2$, followed by acid hydrolysis.

According to the Jewell et al prior art (US 4,677,211), although it does not produce the desired alpha-DFMO product by the process, it expressly discloses

the same reactant and reaction conditions as shown in the claimed process ; for example, the Wittig reagents is prepared by treating a compound of formula X:



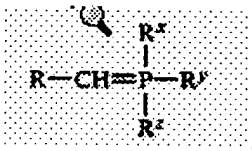
with a strong base at a reduced temperatures from -15^0 to 0^0 C (see col. 5, lines 53-67) ; as a result of the process, the final product is  ,which is not the claimed final alpha-DFMO (difluoromethylornithine).

As the prior art have been discussed in the above, there is no conclusive data that the generic compound without any chemical structural formula would be sufficient enough to lead the desired final product alpha-DFMO (difluoromethylornithine).

The predictability or lack thereof in the art

In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art would recognize that any compound without a general structural chemical formula would result in only the uncertainty of the outcome of the process as shown in Jewell et al prior art (US 4,677,211), which discloses

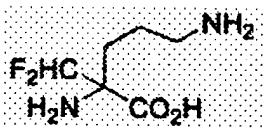
the preparation of the Wittig reagents ; as a result of the process, the final product

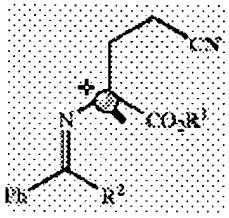
is  , which is not the intended final product of the claimed process. Therefore, the use of a generic phrase "a compound" can not be translated to the production of the claimed product.

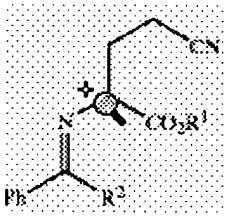
The amount of direction or guidance present

The direction present in the instant specification is that any compound without a general structural chemical formula can be lead to the formation of the desired product. However, the specification is silent and fails to provide guidance as to whether any compound is sufficient enough to allow to form the desired product ; the specification fails to provide a correlation between the structure of the invention and its function. Also, there is no direction and guidance for any compound without a general structural chemical formula to be used for the production of the desired final product.

The presence or absence of working examples

There are only six working examples for producing the claimed alpha-DFMO (difluoromethylornithine) product with a formula of  by

treating the  compound to be reacted with a strong base at a temperature of -35^0 to 25^0 C, wherein $R^1 = CH_3CH_2$, $R^2 = H$.

Furthermore, there are not other working examples for any other compounds different from the  in the specification. Also, the specification fails to provide working examples as to how the other types of compounds can be resulted in the claimed product, i.e. again, there is no correlation between the intermediate and the desired final product.

The breadth of the claims

The breadth of the claims is the treatment of a compound with a strong base at a temperature of -35^0 to 25^0 C without regarding the affect of the different substituents on the compound on the desired final product.

The quantity of experimentation needed

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine which any one of the compounds would be resulted in the claimed desired compound and would furthermore then have to determine which any one of the compounds would not be resulted in the claimed desired compound.

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which intermediates can be employed to produce the desired claimed compound encompassed in the instant claims, with no assurance of success.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1 , the phrase "an intermediate compound comprising fluorine and a nitrile moiety " is recited. This is vague and indefinite because it contains unspecified substituents and the term "comprising" is an open term. The term " comprising " would mean that there are other additional components besides the fluorine and a nitrile moiety present in the intermediate compound. Therefore, an appropriate correction is required.

Claims 1 and 4 , 10 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted step is: how selectively the nitrile is reduced under particular reaction conditions,

such as specific temperature range (25 to 40^0 C) and pressure range (80 to 120 psi), and the use of a specific reagent (hydrogen) and catalyst (transition metal catalyst : palladium on carbon). Therefore, an appropriate correction is required.

In claims 4 and 5, the phrase "a compound comprising an ester or amide" is recited. This is vague and indefinite because it contains unspecified substituents and the term "comprising" is an open term. The term " comprising " would mean that there are other additional components besides an ester or amide present in the compound. Therefore, an appropriate correction is required.

In claim 6, the phrase "a compound comprising fluorine and a moiety " is recited. This is vague and indefinite because it contains unspecified substituents and the term "comprising" is an open term.. The term " comprising " would mean that there are other additional components besides fluorine and a moiety present in the compound. Therefore, an appropriate correction is required.

In claim 7, the phrase "said intermediate compound contains at most one Schiff's base " is recited. This is vague and indefinite because it contains unspecified substituents and the term "contains" is an open term. The term " contains " would mean that there are other additional components besides one Schiff's base present in the compound. Therefore, an appropriate correction is required.

In claim 9, the phrase " Z is (ii) a moiety " is recited. This is vague and indefinite because there is no corresponding formula in the claim ,which requires the variable of "Z". Therefore, an appropriate correction is required.

In claim 10, the phrases "an intermediate compound comprising fluorine and a nitrile moiety" and ' a compound comprising an amine moiety and a second moiety" are recited. These are vague and indefinite because they contain unspecified substituents and the term "comprising" is an open term.. The term "comprising " would mean that there are other additional components besides fluorine and a nitrile moiety present in the intermediate compound and an amine moiety and a second moiety present in the intermediate compound. Therefore, an appropriate correction is required.

Double Patenting

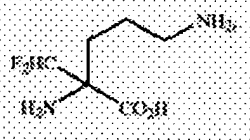
The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

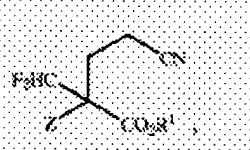
Claims 1-19 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 6-7, 11, 14, 20-23, and 33 of U.S. Patent No. 6,730,809 B2. Although the conflicting claims are not identical, they are not patentably distinct from each other because U.S. Patent No. 6,730,809 B2 does disclose a process for the production of alpha-difluoromethylornithine (DFMO) by selectively reducing a nitrile moiety and further hydrolyzing the remaining product to produce the desired alpha-difluoromethylornithine product in the following claims:

1. A process for the preparation of a compound of the formula



the process comprising:

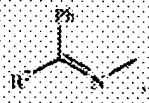
(a) selectively reducing a nitrile moiety of a compound of formula



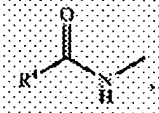
wherein R^1 is linear or branched C_1 to C_4 alkyl and Z is

(i) $-NH_2$ or

(ii) a moiety selected from the group consisting of

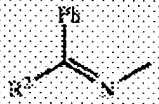


wherein R^2 is hydrogen, linear or branched C_1 to C_4 alkyl or aryl, and

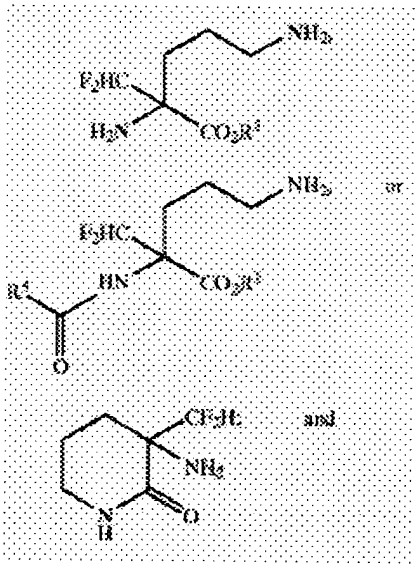


wherein R^5 is linear or branched C_1 to C_4 alkyl, alkoxy or aryl;

(b) if present, hydrolyzing the



moiety, producing, as a result of step (a), or step (a) and step (b), a compound of one of the following formulas

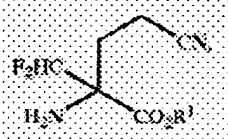


(c) hydrolyzing the ester and amide (including the lactam) moieties of formulas 7, 9, or 10 to give the compound of formula 1.

2. The process of claim 1, comprising the steps of:

(a1) selectively reducing a compound of the formula

6

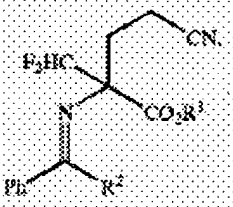


to give the diamino compound of the formula 7 or a salt thereof, and

(c1) hydrolyzing the ester moiety of the diamino compound of the formula 7 to provide the compound of the formula 1.

3. The process of claim 2, wherein the compound of formula 6 is formed by hydrolyzing a Schiff's base moiety of a compound of the formula

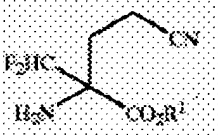
5



6. The process of claim 1, comprising the steps of:

(a2) selectively reducing a compound of the formula

6

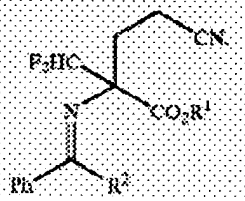


to give the lactam compound of the formula 10; and

(c2) hydrolyzing the lactam compound of the formula 10 to give the compound of the formula 1, or a pharmaceutically acceptable salt thereof.

7. The process of claim 6, wherein the compound of formula 6 is formed by hydrolyzing a Schiff's base moiety of a compound of the formula

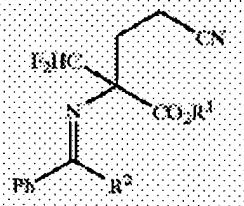
5



11. The process of claim 1 comprising the steps of:

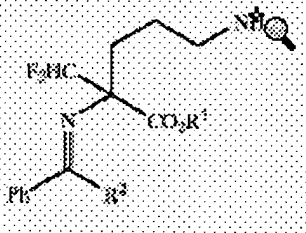
(a3) selectively reducing a compound of the formula

5



to give a compound of the formula

11



or a salt thereof; and

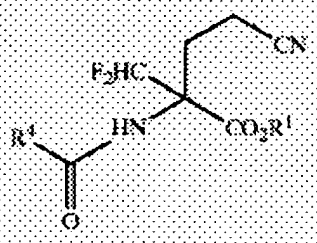
(b3) hydrolyzing the Schiff's base moiety of the compound of the formula 11 under acidic conditions to give the diamino compound of the formula 7, and

(c3) hydrolyzing the ester moiety of the diamino compound of the formula 7 to give the compound of the formula 1.

14. The process of claim 1, comprising the steps of

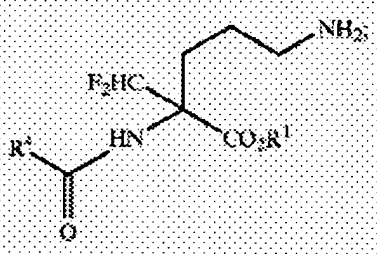
(a4) selectively reducing the nitrile moiety of the compound of formula

8



o give a compound of the formula

9

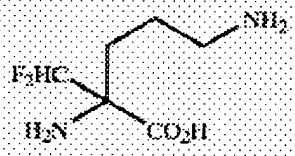


nd

(c4) hydrolyzing the amide and ester moieties of the compound of the formula 9 to give the compound of the formula 1.

20. A process for the preparation of a compound of the formula

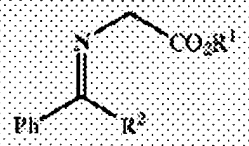
1



or a pharmaceutically acceptable salt thereof, the process comprising:

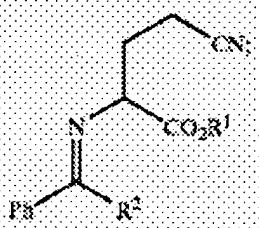
(a) reacting a compound of the formula

3



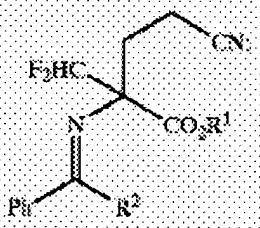
with acrylonitrile or 3-halopropionitrile to give a compound of the formula

4



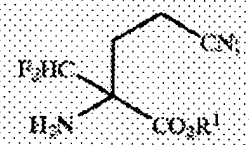
(b) alkylating the compound of the formula 4 with chlorodifluoromethane to give the compound of the formula

5



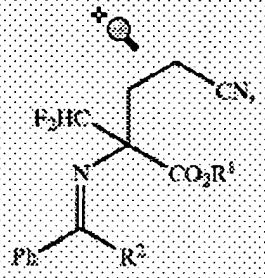
(c) hydrolyzing the compound of the formula 5 to give a compound of the formula

6



21. The process of claim **20**, wherein the alkylation of (b) is performed in the presence of an alkoxide base of the formula MOR^3, wherein R^3 is C_1 to C_4 linear or branched alkyl and M is an alkali metal.

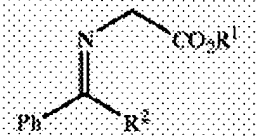
22. A process for the preparation of a compound of the formula



8

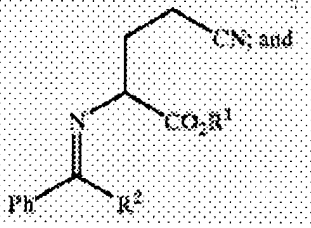
wherein R^1 is linear or branched C_1 to C_4 alkyl and R^2 is hydrogen, linear or branched C_1 to C_4 alkyl or arkyl, the process comprising:

(a) reacting a compound of the formula



2

with an alkylating reagent selected from the group of acrylonitrile and a 3-halopropionitrile to give a compound of the formula

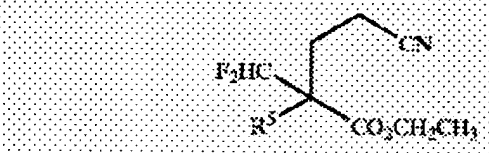


4

(b) alkylating the compound of the formula 4 with halodifluoromethane alkylating agent with an alkoxide base of the formula MOR^3, wherein R^3 is C_1 to C_4 linear or branched alkyl and M is an alkali metal to give the compound of the formula 5.

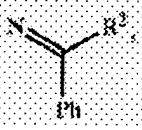
23. The process of claim 22, wherein the alkylation of (b) is performed in the presence of an alkoxide base of the formula MOR^3, wherein R^3 is C_1 to C_4 linear or branched alkyl and M is an alkali metal

33. A compound of the formula



wherein R^5 is:

(a)

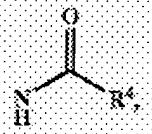


wherein R^2 is hydrogen, linear or branched C_1 to C_4 alkyl or aryl;

(b)

NH_2; or

(c)



wherein R^4 is linear or branched C_1 to C_4 alkyl, alkoxy or aryl.

However, the instant invention differs from the prior art in that the preparation of alpha-difluoromethylornithine performed at a temperature of -35^0 to 25^0 C is unspecified in the prior art claim.

Even so, the prior art specification has disclosed the following limitation (see col. 5 ,lines 17 49-54):

> The alkylation reaction is carried out, for example, by deprotonation at a temperature of from about −35 to about 25° C. Once the α-anion has been generated, the alkylating reagent is introduced and the temperature of the reaction can be, for example, from about −5 to about 20° C. (for R^2=aryl).

From this passage, it becomes clear that the deprotonation in the alkylation reaction takes place at a temperature of -35^0 to 25^0 C in the presence of a strong base before introducing a halodifluoromethane alkylating agent (see col. 5 ,lines 17-19) into the reaction. Therefore , the specific temperature range of -35^0 to 25^0 C in the alkylation reaction is a crucial parameter on the way to accomplishing the production of alpha-difluoromethylornithine. Therefore, it would have been obvious to the skillful artisan in the art to be motivated to introduce the prior art 's alkylation temperature parameter into the currently claims because the skilled artisan in the art would expect such a modification to ensure the successful production of alpha-difluoromethylornithine as guidance shown in the prior art.

Therefore, they are not patentably distinct from each other with respect to the claims of themselves.

Claim Rejections - 35 USC § 102

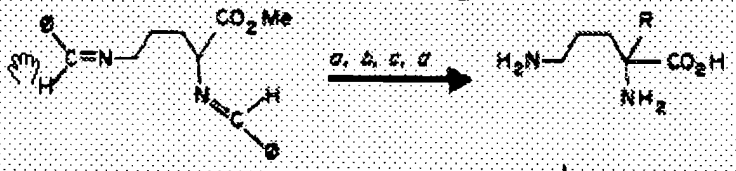
The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 6-7, 9, and 18-19 are rejected under 35 U.S.C. 102(b) as being anticipated clearly by P. Bey et al (J. Am. Chem. .Society , 100 p. 2551-2553, 1978).

P. Bey et al discloses the synthesis of alpha-difluoromethylornithine (DFMO) by regiosselective alkylation of the Shiff base of ornithine methyl ester with chlorodifluoromethane and subsequent acidic hydrolysis below (see page 2552, right col. , the first paragraph) :

Scheme II. Synthesis of Ornithine Analogues 1



1

	R	RX	Overall Yield,[e,f] %	Mp,[g]
1a	CHF_2	F_2CHCl	60	183
1b	CH_2Cl	$ClCH_2Br$	65	140
1c	CH_2CN	$NCCH_2Cl$	12[h]	260

[a] $LiN[CH(CH_3)_2]_2$. [b] RX. [c] 1 M HCl, room temperature, then 6 M HCl, reflux. [d] When R = CH_2CN, stepwise hydrolyses are required; 1 M HCl for removal of the benzylidene groups and NEt_3 in H_2O for cleavage of the methyl ester. [e] Not optimized. [f] Isolated as the monohydrochloride salt; 1a crystallizes with 1 mol of H_2O. [g] Instantaneous from Kofler hot bank. [h] Low yield due to competitive formation of the corresponding piperidone derivative during the basic hydrolysis of the methyl ester.

This is identical with the claims.

Claim Rejections - 35 USC § 103

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that

the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-2, 4-6, 9-10, 12,16, and 18-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seki et al (Biosci., Biotech. Biochem., 57(6), 1024-1025, 1993).

Seki et al discloses a preparation of alpha-difluoromethylornithine (DFMO) from OrnOME-2HCl by using an diisocyanato intermediate prepared via the

formyl derivative and alkylated with $ClCHF_2$, followed by acid hydrolysis in the following detailed steps:

a) fluxing a mixture of ornithine methylester dihydrochloride and a formamide in toluene to produce a N,N'diformylornithine methyl ester compound (1);

b) adding phosphoryl chloride into a mixture of compound (1) and triethylamine and pouring the resultant mixture to aqueous NH_3 in order to obtain methyl 2,5-diisocyanopentanoate compound (2);

c) adding a mixture of chlorodifluoromethane and compound (2) to the suspension of sodium hydride at 10^0 C, thereby isolating methyl 2-difluoromethyl -2,5-diisocyanopentanoate compound (3);

d) stirring a mixture of compound (3) and HCl in methanol at 40-50^0 C to obtain alpha-difluoromethylornithine methyl ester dihydrochloride compound (4);

e) refluxing a mixture of compound (4) and HCl for 4 h and then concentrating the resultant mixture to isolate the alpha-difluoromethylornithine hydrochloride (see page from 1024, right col. 2nd paragraph to page 1025, left col. the first paragraph).

The instant invention, however, differs from the prior art in that the final claimed compound has no hydrochloride salt form unlike the prior art compound.

Even so, it is well-known in the art that it is obvious to form salts from know acids or vise-versa. In re William , 89 USPQ 396 (CCPA 1951). Furthermore, Seki et al does disclose the preparation of the salt form of alpha-difluoromethylornithine (DFMO) HCl, which can easily removed by changing the pH, which is known in the art. If the skilled artisan in the art had desired to form alpha-difluoromethylornithine as an alternative, it would have been obvious to the skilled artisan in the art to be motivated to change from the salt form of alpha-difluoromethylornithine (DFMO) HCl to alpha-difluoromethylornithine. This is because the skilled artisan would have known how to change the pH and remove the acid addition salt .

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Taylor Victor Oh whose telephone number is 571-272-0689. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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